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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ISSAC, ROY P	
ART UNIT	**PAPER NUMBER**
1623	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/619,729	ROLDAN ET AL.	
	Examiner	Art Unit	
	Roy P. Issac	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-46,54,58 and 59* is/are pending in the application.

4a) Of the above claim(s) *47-53 and 55-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-46, 54, and 58-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a divisional of 09/830,734 (July 27, 2001), now U.S. Patent 6,605,603, which is a 371 of PCT/EP99/08269 (October 29, 1999), which claims priority to Argentina P 98 01 05446 (October 30, 1998).

This Office Action is in response to Applicant's amendment/ remarks/ response filed 2/23/2007 wherein claims 32-34, 36, 38, 40-42 and 54 have been amended, and claims 58 and 59 are newly submitted is acknowledged. Claims 32-46, 54, and 58-59 are currently pending. Applicants submission of exhibits Smith et. al, Taber's dictionary page 137 and inserts from Stedman's dictionary are acknowledged.

The following are new grounds of rejection necessitated by applicant's amendments:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32-46, 54, and 58-59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 32, from which claims 33-37 depend is directed to a method for maintaining a healthy bone structure. Applicant's amendment with respect to claim 32

herein has been fully considered, but is deemed to insert new matter into the claims since the specification as originally filed does not provide support for applicants' claim a composition comprising a "medicament comprising a bone health promoting effective amount of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid". The specification as filed provides support for a "*bone-health promoting amounts* of a *medicament*". The claims herein are directed to a "*bone health promoting effective amount of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid*". The scope of a bone health promoting medicament comprising said compound is different from the bone health promoting effective amount of said compound as claimed herein.

Similarly, claim 38 from which claim 39 depends has been amended to recite "a medicament comprising an osteopathy preventing effective amount of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid. The scope of an osteopathy preventing effective amount of a medicament comprising said compound is different from the osteopathy preventing effective amount of said compound as claimed herein. As such, applicant's amendment with respect to claim 38 herein has been fully considered, but is deemed to insert new matter into the claims since the specification as originally filed does not provide support for applicants' claim a composition comprising a "medicament comprising an osteopathy preventing effective amount of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid".

Similarly, claims 40-42 have been amended to recite "a medicament comprising a bone health promoting effective amount of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid. Claims 43-46 and 58-59 depend from claim 42.

The scope of a bone health promoting effective amount of a medicament comprising said compound is different from the bone health promoting effective amount of said compound as claimed herein. As such, applicant's amendment with respect to claim 40 herein has been fully considered, but is deemed to insert new matter into the claims since the specification as originally filed does not provide support for applicants' claim a composition comprising a "medicament comprising a bone health promoting effective amount of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid".

The description as originally filed does not provide support for the claims herein. Consequently, there is nothing within the instant specification which would lead the artisan in the field to believe that Applicant was in possession of the invention as it is now claimed. See *Vas-Cath Inc. v. Mahurkar*, 19 USPQ 2d 1111, CAFC 1991, see also *In re Winkhaus*, 188 USPQ 129, CCPA 1975.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 40 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The recitation of the term "recently" renders the claim indefinite. The term is not clearly defined the specification, and one of skill in the art will not readily recognize which time duration is encompassed by the term "recently." As,

such one of skill in the art will not be apprised on the metes and bounds of the claims herein.

The following are new or modified rejections necessitated by Applicant's amendment filed 2/23/2007, wherein the limitations in pending claims 32-34, 36, 38, 40-42, 54, and 58-59 as amended now have been changed since claims 32-34, 36, 38, 40-42 and 54 were amended, and new claims 58-59 were newly submitted. The limitations in the amended claims have been changed and the breadth and scope of those claims have been changed. Therefore, rejections from the previous Office Action, filed 11/28//2006, have been modified and are listed below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 38-39 and 54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of bone disorders, does not reasonably provide enablement for the prevention of bone disorders or osteopathies as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention:

The current invention relates to the use of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid and for the treatment and prevention of osteopathies and bone disorders as well as the maintenance of healthy bone structure.

The relative skill of those in the art:

The relative skill of those in the art is high, with a typical practitioner having obtained a PhD, M.D. or equivalent advanced degree.

The breadth of the claims:

The claims are considered very broad since they encompass the treatment and prevention of a series of osteopathies and bone disorders including Paget's disease, arthritis, peridental osteopenia, adolescent scoliosis, fracture, disuse osteopaenia, post-transplant osteopenia, metabolic bone disease, osteopenia of prematurity and ossification disorder, a group of diseases with very diverse etiology.

The amount of direction or guidance presented and the presence or absence of working examples:

The specification does not provide any examples of the prevention of any diseases.

The predictability or lack thereof in the art: the instant claimed invention is highly *unpredictable* as discussed below:

Prevention of the series of diseases that can be considered osteopathies and bone disorders including, fracture, arthritis, and metabolic bone disease, is not the same as the treatment of a disease condition. In order to prevent a disease, as opposed to merely delaying or reducing its symptoms, a treatment must either render the subject completely resistant to said disease after a single treatment or a limited number of treatments, or else, when continued indefinitely, continue to completely suppress the occurrence of said disease. In order to practice a preventative method, one of skill in the art must know the answer to several questions in addition to the effectiveness of the therapy in short-term relief of symptoms, including:

1) What is the duration of a single course of therapy? How often must the therapy be administered to completely suppress the disease?

2) Does the subject develop tolerance to the therapy over time? Does the disease eventually progress to a point where the therapy is unable to completely suppress all symptoms?

3) What are the long-term effects of the therapy? Does it cause progressive damage to the kidneys, liver, or other organs? Does the active agent accumulate in the subject's tissues? Is the minimum dose necessary to completely prevent the disease safe for long-term administration? Are there any steps that can be taken to reduce side effects?

For this reason, many of the therapies that are useful for treating a disease are not useful preventing the disease. For example, antibiotics, chemotherapeutics and antiviral drugs are not normally administered to healthy subjects in order to prevent the development of infection or cancer. Thus, it is highly unlikely that any of osteopathies or bone disorders, including arthritis and fracture, can be prevented by the administration of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid of the instant application.

The quantity of experimentation necessary:

In order to determine whether the claimed method can prevent the diverse series of diseases and disorders that can be considered osteopathies and bone disorders, one of ordinary skill in the art will need to answer the questions posed above, which will require significant intellectual and financial input, and an effort that will be collaborative in nature with clinical physicians, organic chemists and biochemists involved, resulting in enormous burden on one of skill in the art to practice the invention as claimed.

Thus, the specification fails to provide clear and convincing evidence in sufficient support for the use of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid for the prevention of any disease condition as recited in the instant claims.

Genentech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors as discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in ***undue experimentation*** to practice the invention commensurate in scope with the claims.

Response to Arguments

Applicant's arguments filed 2/23/207 in regards to this rejection under 35 U.S.C 112, first paragraph, have been fully considered but they are not persuasive.

The applicant's argue that the term ""prevention" in the medical arts refers to methods that lessen the probability or severity of disease". (Applicants response, Page 12). However, none from the numerous dictionary definitions cited by the applicants in their response provide this definition. In page 13 of the response, applicants note that Stedman's Medical Dictionary provides the definition for prevention, *inter alia,* as "anything that arrests the threatened onset of disease". The word arrest is defined as "to stop". (The American Heritage College Dictionary, Page 76; PTO-892). These definitions are not in agreement with applicants proposed description as "methods that

lessen the probability or severity of disease." To "arrest the threatened onset of disease", is to stop the onset of disease, not to "lessen the probability" of onset as applicants assert. Similarly, applicants assertion that ""prevention" refers to a tendency to significantly reduce the incidence or severity of a disease" (Applicant's response, page 17, last paragraph) is also found unpersuasive. Again, to "arrest the threatened onset of disease", is to stop the onset of disease, not to have a "tendency to significantly reduce the incidence or severity of a disease."

Applicants further assert, "U.S. Patent and Trademark Office officially recognizes that the prevention of disease may involve "merely delaying or reducing its symptoms". The applicants' refers to MPEP 708.02 section X in support for this contention. However, MPEP 708.02 does not provide any support for the above quoted statement. MPEP 708.02 does not provide a definition for the term "prevention." Applicants argument is based on one of the requirements to consider an application special, "The petition for special status should be accompanied by a statement explaining how the invention contributes to the diagnosis, treatment or prevention of HIV/AIDS or cancer." Applicants argue that according to the definition put forth in the Office Action, there are no technologies that prevent HIV/AIDS or cancer. Prevention of HIV/AIDS or cancer is irrelevant to this application since the applicants have not claimed HIV/AIDS or cancer. Applicants attention is directed to the entire sentence applicants themselves quoted. "The petition for special status should be accompanied by a statement explaining how the invention contributes to the diagnosis, treatment or prevention of HIV/AIDS or cancer." Based on this statement, an application can be made special if contributes to

the diagnosis or treatment of HIV/AIDS or cancer. There is no need to show that the application is directed to "prevention" of HIV/AIDS or cancer meets the requirements under 35 U.S.C 112 first paragraph at the preliminary stage in order to make an application special.

In response to applicant's review of existing patents, applicant is informed that each patent application is evaluated on its own merits. It is well settled that, allowance of similar claims in another case is immaterial. *In re Giolito*, 530 F.2d. 397. 188 U.S.P.Q. 645 (C.C.PA. 1976).

Applicants citations of exemplifications of the term "prevention" from the publication Steadman's was fully considered but found unpersuasive to remove the above rejection under 35 USC 112, first paragraph. Exemplifications are not clear definitions. The scope of the term prevention is clear from its dictionary definition and exemplifications do not clearly point out what is excluded and included by the term prevention. Applicants submission of the illustrative article by Smith et. al. was fully considered and found unpersuasive. Smith et. al. does not provide a definition for the term "prevention" but rather gives examples of the use of the term. As discussed above, exemplification is not a clear definition. Furthermore, the examiner has not asserted that vaccines are incapable of preventing diseases. As such, applicants arguments in a hypothetical of what the examiner might do in case of the use of vaccines is not relevant to the instant application.

Applicants' argument that the office action adopts an improper standard for enablement was fully considered and found unpersuasive. The applicants assert, "The

Office Action poses particular questions that can only be addressed through direct human experimentation was considered. Office Action, page 5-6." However, the examiner has not required human experimentation, and the questions posed in pages 5-6 don't require human experimentation. Furthermore, the applicants have not pointed out which of the questions will require human experimentation. Without answering the questions presented in pages 5-6, one of skill in the art would not view the invention to be enabled from the prevention of diseases claimed herein. As indicated in the prior office action, the specification is deemed enabled for the treatment of bone disorders. As such, the rejection made under 35 USC 112, first paragraph, is still deemed proper and is adhered to.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 44-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 44-46 recites "after the administration to the patient – the 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid, or any of its soluble salts or any of its hydrates are present at extracellular concentration in a range of between 10^{-6}M and 10^{-10}M" renders the claim indefinite. It is not clear how much of the 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid needs

to be administered to a patient to achieve such extracellular concentration. As such, one of ordinary skill in the art will not be apprised of the metes and bounds of claimed invention.

Response to Arguments

Applicant's arguments filed 2/23/207 in regards to this rejection under 35 U.S.C 112, second paragraph, have been fully considered but they are not persuasive.

Applicants argue that the claimed range of 10^{-10} to 10^{-6} molar is not so vast that a skilled artisan would be unable to avoid infringing by simply taking into account the size of the dosage and the size of the patient. The claimed range herein does not refers to a dosage range of drugs administered to a patient, but rather the range of effect, extracellular concentration achieved by the administration of a drug at some point in time. The specification does not point out any specific range of drugs that can be administered to achieve such an effect or which time point after administering the drug the extracellular concentration is measured. As such, the metes and bounds of the claims herein are not clearly defined. The rejection under 35 USC 112, second paragraph is still considered to be properly made and is adhered to.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 32, 35, 41and 54 are rejected under 35 U.S.C. 102(b) as being anticipated by Van Beek et. al. (WO 97/02827; Of Record).

Beek et. al. discloses the use of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid for the treatment of all forms of osteoporosis, arthritis and periodontal diseases, as well as diagnostic purposes. (Page 3, last paragraph to Page 4, line 2; Page 5, Paragraph 3). Beek et. al. discloses the use of said compound in combination with calcium salt, vitamin D and parathyroid hormone. (Page 4, Paragraph 2; Claims 5-10, Page 15). Beek et. al. further discloses that 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid is devoid of any antiresorptive activity. (Page 5, Paragraph 3, lines 1-5). 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid is disclosed as useful in the treatment of diseases in which antresorptive action is unwanted. . (Page 5, Paragraph 3, lines 5-10). Since the treatment of all forms of osteoporosis and arthritis and periodontal diseases is required "for maintaining a healthy bone structure", said treatment is considered encompassed by the "method for maintaining a healthy bone structure". Example 4 and Figure 1 shows binding of bone mineral by 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid as well as olpadronate at various concnetrations. Example 5 and Figure 2 shows inhibition of calcium incorporation by 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid and similar compounds. Half maximal inhibition for 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid was disclosed as

$2x10^{-7}$M. (Page 11, last paragraph). Van Beek et. al. further discloses that 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid inhibited crystal growth with half maximal concentrations of $3x10^{-6}$ M. (Example 6, page 12). These concentrations are considered to fall in the claimed range of a "bone health promoting effective amount".

Thus, claims 32, 35, 41 and 54 are deemed anticipated by Beek et. al.

Response to Arguments

Applicant's arguments filed 2/23/207 in regards to this rejection under 35 U.S.C 102(b), second paragraph, have been fully considered but they are not persuasive.

The applicants argue that Van Beek only teaches methods of using 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid as carriers for other active compounds against bone disorders such as osteoporosis, arthritis and periodontal diseases. This argument was found unpersuasive since Van Beek clearly teaches the use of 1amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid for bone disorders such as osteopathies, as pointed out and cited in the previous office action. Following is a direct quotation from Van Beek et. al.;

> "Furthermore the invention is related to the use of a 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid of the structural formula, in particular for the diagnosis, prophylaxis and/or treatment of urolithiasis, ectopic calcifications, all forms of osteoporosis, all forms of arthritis and all forms of periodontal diseases."
>
> *Page 3, last paragraph to Page 4, first paragraph, Emphasis added.*

Osteoporosis is clearly a bone disorder and applicants contention that the teachings of Van Beek is limited to the treatment of soft tissues, rather than bone disorders is not

found persuasive. Applicants argument that the teachings of Van Beek is limited to the use of said compound as a biological carrier is also found unpersuasive since the above quotation clearly teaches the use of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid for *diagnosis* and/or *treatment* of bone disorders such as osteoporosis, arthritis and periodontal diseases. Applicants further cites a passage from Van Beek et. al. wherein said compound was disclosed as useful carriers where antiresorptive action is unwanted. However, the above cited passage clearly teaches the use of said compound for the *diagnosis,* and/or *treatment* all forms of osteoporosis, arthritis and periodontal diseases.

Applicant asserts, "nowhere does Van Beek teach that 1-amino-olpadorante itself is useful for the diagnosis, treatment or prevention of bone structure." As shown in the cited passage above, this is clearly not the case. Furthermore, the compound is additionally taught as a carrier for bone and metabolism disorders. (Abstract). As such, the treatment of bone disorders is considered an inherent property associated with the use of said compound as a carrier. There is no need for Van Beek to recognize it as the active agent. Under the principles of inherency, if a prior art device or method, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be anticipated by the prior art device or method. *In Re King* 801 F.2d 1324, 231 USPQ 136 (Fed. Cir. 1986). Note that, "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re

Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) (Applicant argued that the claimed composition was a pressure sensitive adhesive containing a tacky polymer while the product of the reference was hard and abrasion resistant. "The Board correctly found that the virtual identity of monomers and procedures sufficed to support a prima facie case of unpatentability of Spada's polymer latexes for lack of novelty.").

Applicants argue that the "Applicants do not claim 1-amino olpadronate as an inactive ingredient." Note that, "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) (Applicant argued that the claimed composition was a pressure sensitive adhesive containing a tacky polymer while the product of the reference was hard and abrasion resistant. "The Board correctly found that the virtual identity of monomers and procedures sufficed to support a prima facie case of unpatentability of Spada's polymer latexes for lack of novelty."). In this case 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid is taught by Van Beek et. al. for diagnosis and treatment of bone disorders. Whether Van Beek recognized it as an active ingredient is immaterial.

Applicants further argue that as amended the claims herein are limited to "a bone health promoting effective amount" of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid. As noted the disclosed ranges in Figures 1-3

showing the effect of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid in binding bone mineral, inhibition of calcium incorporation and crystal growth are considered to fall in the claimed range herein, "bone health promoting effective amount". Furthermore, since the Office does not have the facilities for preparing the claimed materials and comparing them with prior art inventions, the burden is on Applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald.*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980). The rejection under 35 U.S.C § 102(b) is still deemed proper and is adhered to.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 33-34, 36-40, 42-46 and 58-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Beek et. al. (WO 97/02827; Of record) in view of Brumsen et. al. (Reviews in Molecular Medicine, 76(4), 1997, pp266-283; Of Record).

The disclosure of Beek et. al. is disclosed above in the 102 rejection. Furthermore, Beek et. al. discloses that in comparison with olpadronate, 1-amino-3-

(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid has similar binding activity (Figure 1) while without the undesired antiresorptive activity. (Figure 7; Page 5, Paragraph 3, lines 1-5).

Beek et. al. does not expressly disclose the use of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid for administration to healthy patients or patients without osteopathies or to human being at or above the age of 40 years or to a child or for patients who have undergone corticosteroid treatment or for combating bone disease in a child. Beek et.al does not expressly disclose any extracellular concentraton of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid or the particular dosage ranges claimed herein.

Brumsen et. al. discloses the use of 1-hydroxy-3-(N,N-dimethylamino)-propylidene-1,1-bisophosphonate (olpadronate), a molecule with strong structural similarity to 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid. Note that the only difference between the two compounds is the substitution of the hydroxyl group for the amine group at 1-position. Brumsen et. al discloses that long term olpadronate administration to children severe osteoporosis was devoid of any adverse effect on the growing skeleton. (Web printout; Page 20, Paragraph 2). Brumsen et. al. discloses the use of bisphosphonates for patients who underwent glucocorticoid treatment. (Web printout; Page 21, Paragraph 1). Brumsen et. al further discloses that bisphosphonates are well known for treatment for patients with postmenopausal osteoporosis, a condition generally affecting those above 40 years age.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid to treat children in place of olpadronate because Brumsen et. al. discloses olpadronate for the treatment of children and Beek et. al. discloses 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid to have superior antiresoprtive activity (i.e. lacking the undesired antiresorptive activity) in direct comparison with olpadronate. Furthermore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to treat healthy patients, and patients without osteopathies with 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid because it is devoid of any unwanted antiresorptive activity and beneficial effects. Furthermore, Beek's disclosed use for diagnostic purposes is expected to include healthy individuals as well as individuals without osteopathies. Furthermore, it is considered to be within the basic skills of one of ordinary skill in the art to select appropriate dosage levels for one of various diseases considered as bone disorders. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

One of ordinary skill in the art would have been motivated to use 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid to treat children as well as adults because olpadronate is well known for such treatments and a direct comparison of olpadronate with the compound of the instant application by Beek et. al. disclosed that the compound of the instant application is devoid of antiresorptive activity.

One of ordinary skill in the art would have reasonably expected that the use of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid as claimed herein would be successful because Beek et.al. showed in comparison with olpadronate, the compound of the instant application has similar or better effects.

Thus the invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Response to Arguments

Applicant's arguments filed 2/23/207 in regards to this rejection under 35 U.S.C 102(b), second paragraph, have been fully considered but they are not persuasive.

Applicants argue that as amended the obviousness rejection is moot since Van Beek does not disclose the claim limitation of bone health promoting amount. As discussed in 102 rejection and in the response to arguments following 102 rejection, the concentrations disclosed in Van Beek are considered bone health promoting amounts. Furthermore, it is considered to be within the basic skills of one of ordinary skill in the art to select appropriate dosage levels for one of various diseases considered as bone disorders. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

Applicants further argue that 1-amino-alpadronate is not an obvious variant of olpadronate. Applicants assert, "prior to the instant invention, it was generally believed that 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid was only

useful to serve as mere carrier for more effective compounds when it came to addressing diseases of the bone." As discussed in the 102 rejection and the response to arguments following this contention is not found persuasive in light Van Beek's explicit teaching of the usefulness of said compound for the treatment of all kinds of osteoporosis, arthritis and periodontal diseases.

Applicants further argue that "it was not obvious to use 1-amino-olpadronate for the same purposes for which olpadronate had been used, because 1-amino-olpadronate was known to lack the antiresorptive properties of olpadronate." This argument was found unpersuasive since Van Beek provided direct comparison between olpadronate and the compound of instant application, 1-amino-olpadronate, as pointed out in the previous office action. Van Beek et. al. was cited in the previous office action to show that 1-amino-olpadronate was devoid of the undesired antiresorptive activity. Furthermore, examples 4-6, and figures 1-2 show similar activity between olpadronate and 1-amino olpadronate in case of binding of to bone minerals, inhibition of calcium incorporation and inhibition of crystal growth. Van Beek et. al. further states that, "The bisphonates with an amino substitution at R1 exhibited physiochemical properties (binding to bone mineral, inhibition of calcium incorporation to bone, inhibition of crystal growth) comparable to their respective hydroxyl analogs (see Exmaple 4 to 7)." Since the amino-substituted bisphonates including 1-amino-olpadronate is referred to Van Beek to have similar physiochemical properties one of ordinary skill in the art will clearly expect it to have effectiveness similar to olpadronate. As such, the rejections made under 103(a) are still deemed proper and are adhered to.

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Roy P. Issac whose telephone number is 571-272-2674. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

4/19/07

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